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(54) Title: METHOD FOR A PROGRAMMED CONTROLLED OVARIAN STIMULATION PROTOCOL

(57) Abstract

A method of therapeutic management of infertility by programming of controlled ovarian stimulation (COS) and assisted reproductive procedures (ART) the improvement consisting of a) supression of premature ovulation with an LHRH–antagonist in controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) with multiple follicle and oocyte development; b) programming the start of controlled ovarian stimulation (COS) by the administration of progestogen only – or alternatively combined oral contraceptive preparations; c) exogenous stimulation of the ovarian follicle growth; d) ovulation induction with HCG, native LHRH, LHRH–agonists or recombinant LH; e) application of assisted reproduction techniques, especially of IVF, ICSI, GIFT, ZIFT or by intrauterine insemination by sperm injection.

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Method for a programmed controlled ovarian stimulation protocol

Field of Invention

Women are fertile for a limited time only. Unwanted childlessness occurs in one of 10 couples. The reason for unfulfilled wish for children is related to female factors, e. g. blocked or missing tubes, polycystic ovary disease, or to male factors, e. g. insufficient sperm motility.

To overcome this problem, female partners of infertile couples undergo ovarian stimulation with gonadotropins like HMG (human menopausal gonadotropin), FSH (follicle stimulating hormone) or by the antioestrogen clomiphene and gonadotropins. This therapy stimulates the growth of a cohort of 6 – 12 follicles and oocytes to guarantee the fertilisation of sufficient oocytes by highly specified laboratory technologies. During this procedure a premature ovulation indicated by an LH and progesterone surge is prevented by the administration of LHRH-analogues, either by LHRH-antagonists or by LHRH-agonists.

Background Information and Prior Art

According to the known treatment protocols HMG is given on day 2 of the menstruation cycle. A single or multiple dose of 0,25mg to 5mg of LHRH antagonist Cetrorelix was administered to prevent LH surges on day 5 until and including the day of ovulation induction with HCG. (Hum. Reprod. 1994 May;9(5):788-91, Hum. Reprod. 1995 Jun;10(6):1382-6, Fertil. Steril. 1997;67:917-22, Hum. Reprod. 1998 Sep;13(9)2411-4)

In the PCT application W0 98/58657 the LHRH antagonist ganirelix in an amount of 0,125 -1 mg is administered in the method to prevent premature LH surges in women undergoing controlled ovarian hyperstimulation in combination with exogeneous FSH.

The EP 161 063 also teaches the use of a gonadotropin releasing hormone antagonist to prepare a pharmaceutical composition comprising a gonadotropin selected from HMG and FSH in the treatment of female infertility to suppress estrogen variability, in which treatment the antagonist composition is administered in an effective amount cojointly with the gonadotropin composition.

Usually for controlled induction of ovulation and final follicle maturation HCG (human chorionic gonadotropin) is given. 36 hours thereafter oocytes are picked up (OPU) by transvaginal or laparoscopic follicle puncture.

For the fertilisation of multiple oocytes by the sperms of the male partner assisted reproductive techniques (ART) are applied like IVF (in-vitro-fertilisation), ICSI (intracytoplasmic sperm injection), GIFT (gamete intra-Fallopian transfer) or ZIFT (zygote intra-Fallopian transfer) in highly specialized laboratories on the day of OPU.

Normally, two to four days after extracorporeal fertilization embryo transfer is performed by the replacement of several embryos into the cavum uteri to obtain pregnancy.

As many follicles develop following controlled ovarian stimulation therapy (COS) ovarian enlargement occurs and many oocytes are picked up. Therefore, oocyte pick up procedures have to be done in the operating theatre and with the application of general or regional anesthesia.

Assisted reproductive techniques are carried out in highly specialized laboratories by qualified personnel thereafter.

Preferably, these procedures have to be included into the routine operating theatre plans from Mondays to Fridays. The performance of oocyte pick up as well as of embryo transfer on weekends or holidays is avoided due to lack of enough qualified personnel on duty in most clinics. Furthermore, some hospitals undertake these

procedures only on a few days each month in order to have the oocyte pick up and fertilization procedures performed by a highly specialized serviceteam to increase the number of oocytes obtained as well as the fertilization rates and the number of good quality embryos. Therefore, programmed ovarian stimulation protocols are applied.

Object of the Invention

The present invention especially relates to the improvement of the method of programming of ovarian stimulation procedures, i. e. the administration of LHRH-antagonists in controlled ovarian stimulation where the start of menstrual cycle and ovarian stimulation was programmed.

Summary of the Invention

In a controlled ovarian stimulation procedure conducted with an LHRH–antagonist for the prevention of premature ovulation, gonadotropin injection is started at cycle day one to three of a menstrual cycle and is continued until the day of HCG when enough big follicles have developed.
The LHRH–antagonist is given at the days of risk of premature ovulation.
The duration of ovarian stimulation takes normally ten days in these treatment cycles.

In order to perform oocyte pick up and fertilization procedures during Mondays to Fridays the start of a menstrual cycle and of COS are programmed.
For the programming of the start of the menstrual cycle and of controlled ovarian stimulation procedures oral contraceptives or progestogen-only containing preparations are given in the follicular phase, preferably starting at menstrual cycle day 1 or 2 , or in the late luteal phase of the previous menstrual cycle.
The LHRH antagonist Cetrorelix was also used successfully for this purpose previously when 1mg were given in the luteal phase and luteal regression was obtained and menses started 2 to 4 days later.
The duration of oral contraceptive or progestogen administration will be a minimum of

ten up to a maximum of 25 days. Intake of the last tablet will preferably be on a Monday to Thursday to obtain start of menstrual bleeding and of ovarian stimulation therapy on Fridays to Mondays. Thereafter, oocyte pick up and further ART procedures can be scheduled and undertaken on Mondays to Thursdays.

The in a controlled ovarian stimulation procedure applied LHRH–antagonist for the prevention of premature ovulation can be for instance cetrorelix, teverelix, ganirelix antide or abarelix.

It is further in scope of the invention that the programming of COS and ART procedures is performed by oral administration of progestogen preparations, ethinylestradiol and progestogen, combined mono- bi- and triphasic contraceptive preparations containing contraceptive preparations, mestranol and progestogen, as well as by subcutaneous injection of LHRH antagonists.

The LHRH antagonists may be cetrorelix, teverelix, ganirelix, antide or abarelix and should be administered during the luteal phase in a dosage of 0,5 mg to 10 mg .

The ovarian stimulation is performed by administration of urinary or recombinant FSH or HMG, with or without recombinant LH and with antioestrogens as for example clomiphene also with a combination of antioestrogens as for example clomiphene with gonadotropins.

Example

Material and methods

A total of 30 patients, 15 from each German study center was enrolled for one treatment cycle. In the pre-treatment cycle , each patient received monophasic oral contraceptive(OC) pills containing 30 µg Estradiol in combination with levonogastrel. Gonal-F ® administration starting at dose 150 IU or 225 IU began on the first day of withdrawal bleeding after OC treatment. Cetrotide ® 0,25 mg was given daily from the evening of stimulation day (s-day) 5/morning of s-day 6 until the day before hCG administration. On the basis of the ultrasound scans performed on s-day9/10(s-day 9/10), and a calculation of follicular growth of 2mm per day, hCG was administered to trigger ovulation (when >2 follicle's ≥ 18 mm) were visualized.

Efficacy endpoint assessed included number of follicles ≥ 18 mm on s-day 9/10, total number of vials of Cetrotide ® and ampoules of Gonal-F ® used, duration of Cetrotide ®and Gonal-F ® treatments, number of patients receiving hCG, patients undergoing oocyte retrieval, number of oocytes retrieved, reliability of prediction of day of oocyte retrieval, and pregnancy rate. Safety end-points were indicated and severity of adverse events.

Results

Preliminary results from 17 patents show that the mean number of follicles ≥ 18 mm on s-day 9/10 was 2,2. On the last day of Cetrotide® administration the mean number of follicles with diameters of ≤ 14 mm, 15 -17 mm and ≥18 mm were 2,7, 4,9 and 2,7 respectively. A median number of 24 ampoules of Gonal-F® equivalent to 75 IU were administered for 10,0 days, and daily injections of Cetrotide® 0,25 mg were administered for 5,7 days on average, respectively. All 17 women who received hCG had ovum pick up and embryo transfér. Overall, a mean number of 8,8 oocytes were retrieved and a mean of 2 embryos was transferred.

The pregnancy rate per attempt/cycle was 41%.The difference between predicted and actual day of OPU was 2 day on average. There as no cases of OHSS nor adverse events.

Conclusions

This is the first result of the use of Cetrotide® in COS cycles programmed by OCs. Overall, the stimulation results are similar to those observed in non-programmed cycles. Cetrotide® appears to be effective in OC programmed cycles ,is well tolerated and allows reliable prediction of the day of oocyte retrieval. Thus use of Cetrotide ® in programmed stimulation cycles represents another step towards well – tolerated , effective and convenient procedures in ART.

Cetrotide ® is the registered Trade Mark for the LHRH Antagonist cetrorelix.

The various embodiments which have been described herein intended to be representative and not limiting, as various changes and modifications can be made in

the present invention without departing from the spirit and scope thereof.

Claims :

1.In the method of therapeutic management of infertility by programming of controlled ovarian stimulation (COS) and assisted reproductive procedures (ART) the improvement consisting of

a) suppression of premature ovulation with an LHRH-antagonist in controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) with multiple follicle and oocyte development

b) programming the start of controlled ovarian stimulation (COS) by the administration of progestogen only - or alternatively combined oral contraceptive preparations

c) exogenous stimulation of the ovarian follicle growth

d) ovulation induction with HCG, native LHRH, LHRH-agonists or recombinant LH

e) application of assisted reproduction techniques, especially of IVF, ICSI, GIFT, ZIFT or by intrauterine insemination by sperm injection.

2. The method of claim 1 wherein in order to perform oocyte pick up and fertilization procedures during Mondays to Fridays the start of a menstrual cycle and of COS are programmed.

3. The method of claim 1 wherein the programming of the start of the menstrual cycle and of controlled ovarian stimulation procedures oral contraceptives or progestogen-only containing preparations are given in the follicular phase, preferably starting at menstrual cycle day 1 or 2 or in the late luteal phase of the previous menstrual cycle.

4. The method of claim 1 wherein the intake of the last tablet will preferably be on a Mondays to Thursdays to obtain start of menstrual bleeding and of ovarian stimulation therapy on Fridays to Mondays and thereafter, oocyte pick up and further ART procedures can be scheduled and undertaken on Mondays to Thursdays.

5. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is cetrorelix.

6. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is teverelix.

7. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is ganirelix.

8. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is antide.

9. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is abarelix.

10. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of progestogen preparations.

11. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of progestogen- only containing contraceptives.

12. The method of therapeutic management of infertility by programming of COS and

ART procedures according to claim 1 in which the programming is achieved by oral

administration of combined monophasic contraceptive preparations containing ethinylestradiol and progestogen.

13. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is undertaken by oral administration of biphasic contraceptive preparations containing ethinylestradiol and progestogen.

14. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of triphasic contraceptive preparations containing ethinylestradiol and progestogen.

15. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of contraceptive preparations containing mestranol and progestogen.

16. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist cetrorelix with a dosage of 0,5 to 10 mg administered during luteal phase .

17. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist teverelix with a dosage of 0,5 to 10 mg administered during luteal phase .

18. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist ganirelix with a dosage of 0,5 to 10 mg administered during luteal phase.

19. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist antide with a dosage of 0,5 to 10 mg administered during luteal phase.

20. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist abarelix with a dosage of 0,5 to 10 mg administered during luteal phase .

21. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the stimulation is performed by administration of urinary or recombinant FSH or HMG, with or without recombinant LH.

22. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the ovarian stimulation is achieved with antioestrogens as for example clomiphene.

23. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the ovarian stimulation is achieved with the combination of antioestrogens with gonadotropins.

24. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the ovarian stimulation is achieved with the combination of clomiphene with gonadotropins.

INTERNATIONAL SEARCH REPORT

In itional Application No
PCT/EP 00/02466

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K38/24 A61P15/08 //(A61K38/24,38:09,31:565)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EMBASE, BIOSIS, MEDLINE, CHEM ABS Data, EPO-Internal, CANCERLIT, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALBANO C. ET AL: "Hormonal profile during the follicular phase in cycles stimulated with a combination of human menopausal gonadotrophin and gonadotrophin-releasing hormone antagonist (Cetrorelix)." HUMAN REPRODUCTION, (1996) 11/10 (2114-2118). , XP002075394 abstract	1-14
Y	CA 2 200 541 A (ASTA MEDICA AG) 22 July 1998 (1998-07-22) abstract; claims	1-24
Y	EP 0 788 799 A (ASTA MEDICA AG) 13 August 1997 (1997-08-13) claims	1-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
4 August 2000	23/08/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BOUCHARD P ET AL: "Endocrine features of combined gonadotropin and GNRH antagonist ovulation induction" OVULATION INDUCTION: UPDATE: THE PROCEEDINGS OF THE WORLDCONGRESS ON OVULATION INDUCTION,XX,XX, 1998, pages 115-119-119, XP002111491 the whole document	1-24
Y	FELBERBAUM, R. ET AL: "Multiple dose protocol for the administration of GnRH-antagonists in IVF: the "Lubeck-protocol"" IN VITRO FERT. ASSISTED REPROD., PROC. WORLD CONGR. (1997), 397-404. EDITOR(S): GOMEL, VICTOR;LEUNG, PETER C. K. PUBLISHER: MONDUZZI EDITORE, BOLOGNA, ITALY. , XP000933573 page 400, paragraph 3 -page 403, paragraph 2	1-24
Y	VIDAL L: "DICTIONNAIRE VIDAL, 71. EDITION. PASSAGE-TEXT" , DICTIONNAIRE VIDAL,FR,PARIS, EDITIONS DU VIDAL, VOL. ED. 71, PAGE 930 XP002144115 page 930, column 2 -column 3	1-24

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-24

Present claims 1-24 relate to a method of therapeutic management defined (inter alia) by reference to following desirable characteristics or propertys, namely " LHRH-antagonist", " progestogen or alternatively combined oral contraceptive", "exogenous stimulation of the ovarian follicle growth", "ovulation induction with HCG, native LHRH, LHRH-agonists or recombinant LH" and " application of assisted reproduction techniques".

The claims cover all methods combining those characteristics or propertys, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the method described in the example of the description at page 4 an 5, with due regard to the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir. ational Application No
PCT/EP 00/02466

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CA 2200541 A	22-07-1998	NONE	
EP 0788799 A	13-08-1997	JP 9227404 A	02-09-1997

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